**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**PATENT APPLICATION EXAMINING OPERATIONS**

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| Appl. No. | : 10/516,405 | Confirmation No. 2828 |
| Applicant | : Demmer *et al.* | |
| Filed | : November 30, 2004 | |
| Title: | : Membrane, Device And Method For Removing Proteases From Liquids | |
| TC/A.U. | : 1651 | |
| Examiner | : Fernandez, Susan Emily | |
| Docket No. | : 9013.0099 | |
| Customer No. | : 00152 | |

**APPEAL BRIEF**

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October 10, 2008

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

## Real Party in Interest

The real party in interest is the assignee Sartorius Stedim Biotech GmbH, a German corporation.

## Related Appeals or Interferences

Serial No. 11/436,861 is a divisional of the instant application and is on appeal from a final rejection by the same Examiner.

## Status of Claims

Claims 1-10 and 12 have been cancelled. Claims 11 and 13-15 stand rejected and are appealed. Claim 16 is objected to as being dependent from a rejected base claim. A copy of all pending claims is set forth in Claims Appendix.

## Status of Amendments

The last amendment, filed April 15, 2008, has been entered.

## Summary of Claimed Subject Matter

The invention claimed in independent claim 11, from which claims 13-15 all depend, is a device for removing proteases from biological fluids and pharmaceutical solutions comprising a housing with a fluid inlet and a fluid outlet, the housing containing a plurality of functionalized microporous membranes arranged in series wherein the membranes contain functional groups that are chemically coupled with at least one protease inhibitor capable of selectively binding an acid protease, a metalloprotease, a cystein protease, or a serine protease selected from TLCK and p-aminobenzamidine (page 4, lines 15-24; FIG. 1).

Claim 15 is directed to a method for removing proteases from fluids comprising feeding a protease-containing fluid to the device of any of claims 11, 13 or 14 (page 2, lines 31-32; Examples 1 and 2).

## Ground of Rejection to be Reviewed on Appeal

The only issue for review is the propriety of the obviousness rejection of claims 11 and 13-15 as being unpatentable over Grano *et al.* (**Grano**) in view of Burtin *et al.* U.S. Patent No. 6,248,238 (**Burtin**) and Bergmann U.S. Patent No. 5,168,041 (**Bergmann**).

## ARGUMENT

### Prior Art Relied Upon

**Grano** discloses in pertinent part the serine protease inhibitor alpha-antitrypsin coupled to a microporous polyethersulfone membrane via grafted glycidyl methacrylate and a phenylenediamine (PDA) spacer between the grafted membrane and the protease inhibitor, with the protease inhibitor in turn being coupled to the PDA by diazotization. See pages 298-299 and Fig. 1. There is no disclosure or suggestion of coupling any other protease inhibitor and in particular not one capable of coupling an acidic protease, a metalloptrotease, or a cysteine protease, as claimed in claim 11. Likewise there is no disclosure of the serine protease inhibitors TLCK or p-aminobenzamidine, also as claimed in claim 11.

**Burtin** discloses apparatus (such as a dialyzer) consisting of a housing, a fluid inlet and a fluid outlet for the extracorporeal treatment of blood or plasma, the apparatus incorporating a membrane consisting of at least one electronegative polymer so as to render the surface of the membrane negatively charged. Abstract and Column 4, lines 33-38. The membrane has a single cationic anti-protease agent (the anticoagulant nafamostat mesylate) electrostatically bound to the negatively charged sites within or on the surface of the membrane. Column 4, lines 40-45 and 53-56; Examples.

**Bergmann** lists in Table 1 four of the protease inhibitors recited in claim 13, i.e., pepstatin, bestatin, EDTA and leupeptin. None of them are disclosed or suggested to be either chemically coupled to a membrane or even to be suitable for chemical coupling to any membrane. Such protease inhibitors were tested along with 16 others as to their effectiveness in

suppressing the breakdown of the human bone protein osteocalcin *in vitro*. Column 3, line 60 through column 4, line 12; column 6, line 20 through column 7, line 22. The purpose of measuring the suppression of breakdown of osteocalcin is to indirectly measure the concentration of osteocalcin in human blood in order to study bone metabolism. Column 1, lines 1-3, 31-37 and 40-44. Thus, the entire thrust of Bergmann has nothing to do with the removal of proteases from fluids, as claimed by appellant. Query whether Bergmann may even be considered analogous art. See *In re Clay*, 23 USPQ 2d 1058 (Fed Cir 1982).

**Obviousness of Claims 11 and 13-15**

Claim 11 is the only independent claim in the application, with claims 13-15 depending therefrom; claim 15 also depends from claim 13 or 14. Thus, if claim11 is not rendered obvious by the combination of Grano, Burtin and Bergmann, neither are claims 13-15.

There are six limitations in claim 11 that are not disclosed by the primary reference Grano: (1) a chemically coupled protease inhibitor capable of selectively binding an acid protease; (2) a chemically coupled protease inhibitor capable of selectively binding a metalloprotease; and (3) a chemically coupled protease inhibitor capable of selectively binding a cysteine protease; (4) a chemically coupled protease inhibitor capable of coupling either of the serine proteases TLCK or p-aminobenzamidine; (5) a housing having a fluid inlet and a fluid outlet; and (6) a housing containing a plurality of membranes arranged in series.

The Examiner concedes in the final rejection that Grano does not disclose limitations (5) and (6). Final Rejection, page 3, second full paragraph. As to limitation (5), the Examiner contends that Burtin supplies this teaching, which is conceded for purposes of argument. But as to limitation (6), the Examiner reasons that it would have been obvious "to

have used the Grano membranes [*sic*] in a series in a medical apparatus for the... treatment of blood... since Burtin et al. demonstrates that protease inhibitors [*sic*] on membranes [*sic*] in a housing with a fluid inlet and a fluid outlet is suitable for treatment of blood. Further more [*sic*], the use of multiple membranes in a series would have ensured thorough reduction of the active protease blood concentration." Final Rejection, page 3, last paragraph.

There are at least five gaps in the factual underpinning of the Examiner's reasoning. First, Grano does not disclose "membranes," but rather a single membrane. Second, Grano's membrane is not one which is claimed in claim 11. Third, Burtin does not disclose "protease inhibitors," but rather the single protease inhibitor nafamostat mesylate. Fourth, Burtin does not disclose "membranes" in a housing, but rather a single membrane. Fifth, neither Grano nor Burtin nor Bergmann disclose or suggest the use of membranes in a series.

As to limitations (1)-(4) of claim 11 noted above, the Examiner points to nothing in the prior art where such limitations are found. In any event, the secondary references Burtin and Bergmann do not disclose or suggest any chemical coupling of any protease inhibitor to any substrate whatsoever, let alone chemical coupling to a membrane of any of the three specific classes (acidic protease, metalloprotease and cystein protease) and two specifically named (TLCK and p-aminobenzimadine) protease inhibitors in claim 11. Without more, the obviousness rejection is improper.

And the Bergmann reference has no value as a teaching reference since it merely lists protease inhibitors tested for effectiveness in an unrelated application, but that fall within the three classes claimed in claim 11 and four of the specific protease inhibitors recited in claim 13.

As stated by the Supreme Court, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l v. Teleflex Inc.*, 127 S Ct 1727, 82 USPQ 2d 1385, 1396 (2007).

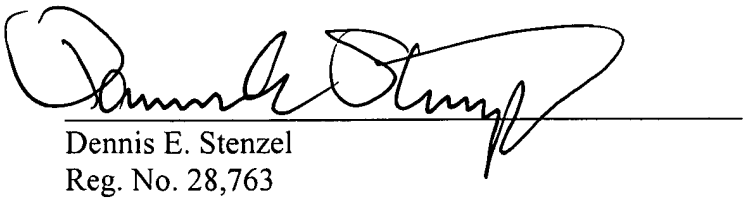
Since claims 13-15 all depend from claim 11, they incorporate the same limitations as that claim, and so are distinguishable from and not rendered obvious by the cited prior art for the reasons stated above.

In summary, the Examiner has simply not articulated any "reasoning with some rational underpinning" to support her conclusion that the combination of Grano, Burtin and Bergmann renders claims 11 and 13-15 obvious. See *In re Kahn,* 78 USPQ 2d 1329 (Fed Cir 2006).

**Conclusion**

Because the combination of Grano, Burtin and Bergmann does not render any of claims 11 or 13-15 obvious, the final rejection of those claims should be reversed and they should all be allowed.

Respectfully submitted,



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**CERTIFICATE OF MAILING**

I hereby certify that this APPEAL BRIEF is being deposited with the United States Postal Service as first class mail on the date indicated below in an envelope addressed to: MAIL STOP APPEAL BRIEF - PATENTS, Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

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Dennis E. Stenzel

## CLAIMS APPENDIX

11. A device for removing proteases from biological fluids and pharmaceutical solutions comprising a housing having a fluid inlet and a fluid outlet, said housing containing a plurality of membranes arranged therein in series, wherein said membranes each consist essentially of a functionalized microporous membrane body containing functional groups chemically coupled to at least one protease inhibitor that is capable of selectively binding a protease selected from the group consisting of an acidic protease, a metalloprotease, a cysteine protease and a serine protease, said serine protease inhibitor being selected from the group consisting of TLCK and p-aminobenzamidine.

13. The device of claim 11 wherein said protease inhibitor capable of binding with an acidic protease is pepstatin; said protease inhibitor capable of binding with a metalloprotease is selected from the group consisting of bestatin, diprotin and EDTA; and said protease inhibitor capable of binding with a cysteine protease is selected from the group consisting of antipain, chymostatin, leupeptin and E64.

14. The device of claim 11 wherein said membranes each contain two different protease inhibitors.

15. A method for removing proteases from fluids comprising feeding a protease-containing fluid to the device of any of claims 11, 13 or 14.

## CLAIMS APPENDIX, ctd.

16. The device of claim 11 wherein said protease inhibitor capable of binding with a serine protease is selected from the group consisting of TLCK and p-aminobenzamidine and said functional groups are epoxy groups.

## EVIDENCE APPENDIX

Not Applicable

## RELATED PROCEEDINGS INDEX

Not Applicable